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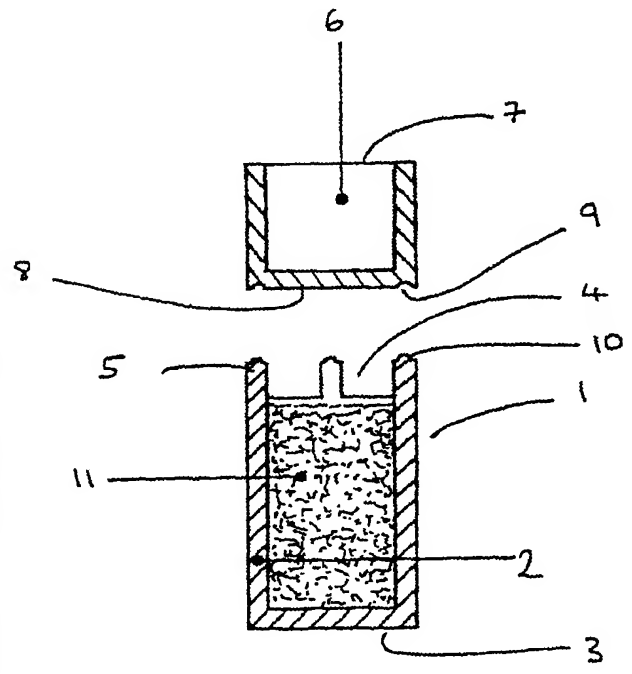
(54) Title: DOSAGE UNIT FOR DRY POWDER MEDICAMENT



(57) Abstract: There is described a medicament dosage unit (1) comprising a sleeve (12) and a medicament holding chamber (2) adapted to form a slidable fit within the sleeve (12), the sleeve (12) and the chamber (2) being dimensioned such that the sleeve (12) extends beyond the length of the chamber (2), and the unit being provided with an openable closure member (6). There is also described a cartridge comprising (112) a plurality of such dosage units and a delivery device adpated for the use of individual dosage units of a cartridge.

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DOSAGE UNIT FOR DRY POWDER MEDICAMENT

This invention relates to a novel form of drug container and to medical devices and methods of treatment utilising such containers.

International Patent Application No WO93/16748 describes an inhalation device and in particular a dry powder inhaler, known as TECHNOHALER being developed by Innovata Biomed in the UK. The TECHNOHALER is provided with a plurality of capsules, usually in the form of a cartridge, wherein each capsule contains a single metered dose of medicament. The capsule of the prior art generally is made up of a spool and a spool carrier. The spool comprises a longitudinal body and terminal flanges at each end. The sides of the flanges form a seal and a tight slidable fit with the inner walls of the spool carrier. The length of the spool and the length of the spool carrier are substantially the same and medicament fills the space between the spool and the internal walls of the spool carrier.

Furthermore a dry powder inhaler such as TECHNOHALER is provided with suitable indexing means, including a push button and a ratchet mechanism which engages with the upper surface of the container. In TECHNOHALER depression of the push button urges a push rod to act against the spool which is nearest to the inhalation passage of the inhaler and into the inhalation passage.

The spool is pressed out of the spool carrier releasing medicament. The spool is not fully ejected from the spool carrier so that upon rotation of the cartridge the spool is transferred to a waste chamber. Nevertheless, in order to ensure all of the medicament in the capsule is ejected into the inhalation passage the spool must undergo considerable displacement by being pushed close to being ejected from the carriers.

We have now found a novel medicament metered dosage unit which is advantageous in that, inter alia, only a minimal amount of displacement is required for the dispensing of the medicament.

Thus according to the invention we provide a medicament dosage unit comprising a sleeve and a medicament holding chamber adapted to form a slidable fit within the sleeve, the sleeve and the chamber being dimensioned such that the sleeve extends beyond the length of the chamber, and the unit being provided with an openable closure member.

The dimensions of the medicament chamber may be varied, permitting different dosages of medicament to be administered. Preferably, the dimensions are such that the chamber will be filled to provide a single desired dose. In one embodiment the chamber is a substantially elongate member eg a cylindrical member with an open end and a closed end. When the closure member comprises a removable cap, the cap may rest on the sleeve. However, preferentially, the chamber may be provided with one or more spacers at its open end. Preferably at least two spacers are present to allow even resting of the cap. The use of spacers is advantageous in that they prevent the cap from coming into contact with the medicament and possibly reducing the accuracy of the dosage delivered. The spacers can also act to enhance removal of the cap. The spacers may optionally be provided with a ridge upon which the cap may rest.

The cap may generally be the same diameter as the medicament chamber. The cap may comprise a flat disc, a plug or an inverted cup. It is desirable that the cap should provide a closed face abutting the chamber and/or spacers. The length of the cap will be small relative to the length of the chamber.

The sleeve is adapted to form a snug fit at least around the joint formed between the open end of the container and the cap. The sleeve preferentially wraps around the whole of the circumference of the joint so as to form a seal. The sleeve comprises a substantially resilient material, e.g. a plastics sleeve, in order for the inner walls of the sleeve to be biased towards the joint so as to form a sealing engagement. In a preferred embodiment a longitudinal sleeve is used enabling it to also act as a support for the body of the chamber. Thus, it is preferred that the length of the sleeve will be substantially the same as the length of the chamber. In an especially preferred embodiment the length of the sleeve is such that it forms a snug fit with the chamber with only the spacers protruding from the sleeve. When the cap is placed upon the spacers and urged against the chamber so that the container is partially pushed through the sleeve, the closed end of the container protruding from the sleeve and the sleeve forming a sealing engagement with the cap and the container.

When the closure member comprises a cover, the cover is preferably fixed to the sleeve. The cover will generally be the same diameter as the sleeve or, optionally, it may be of slightly greater dimensions such that it overlaps the end of the sleeve. The cover may preferentially comprise any frangible material. Materials which are impermeable to moisture and/or are moisture resistant are preferred. Such materials include, but are not limited to, plastics films or foils, e.g. aluminium foil material. In the case of a plastics cover, this may simply be heat bonded to the sleeve, whilst with a foil cover, a layer of conventionally used adhesive may be used to bond the foil to the sleeve.

The dosage unit may also be one of a plurality of such units arranged in series, which units are able to transfer a succession of metered doses of medicament into the inhalation

passage of a dry powder inhaler. When a plurality of dosage units are connected together, the sleeves required may be comprised of a cartridge with a plurality of sleeves arranged around its periphery. In such a case the dosage units themselves may be connected together or it may be that the sleeves are connected together, or both.

The invention thus also provides a plurality of dosage units arranged in series, each unit being as hereinbefore described. The units may be releasably or permanently attached to one another so as to be in a chain-like conformation, preferably a flexible or semi-flexible chain. The design of dosage units in accordance with the invention makes such flexibility possible.

A series of dosage units in accordance with this aspect of the invention is ideal for use in an inhaler, because it allows sequential presentation of doses of a medicament to the inhalation passage of the inhaler as the series is indexed through the inhaler. If the series is in the form of a flexible chain, it can then be rolled or folded up for compact storage in the inhaler. The series may be of any appropriate length. It may, for instance, be supplied in a length greater than might be needed for use in an inhaler, but capable of being broken up into usable lengths. In an especially preferred embodiment the plurality of dosage units are contained in a cartridge and such a cartridge forms a further aspect of the invention.

In use, when placed in an inhaler, such as the TECHNOHALER, a push rod can act upon the closed end of the container protruding from the sleeve, urging the container back in the sleeve, and causing the cap to be ejected from the other end of the sleeve. When the container is in the inverted position, that is, the closed end uppermost, the cap falls away and the container empties the medicament into the inhalation passage of the inhaler.

Thus, according to a further feature of the invention we provide a medicament delivery device comprising medicament a dosage unit as hereinbefore described. In a most preferred embodiment the medicament delivery device of the invention is an inhaler, e.g. a dry powder inhaler. Thus we especially provide an inhaler as hereinbefore described comprised a plurality of medicament dosage units.

Thus, according to a further feature of the invention we provide dry powder inhaler comprising medicament a dosage unit as hereinbefore described. In a further embodiment we provide an inhaler as hereinbefore described comprised a plurality of medicament dosage units.

In the inhaler of the invention the medicament dosage units are preferably presented in a cartridge as hereinbefore described.

In a preferred embodiment a dry powder inhaler is provided with suitable indexing means, including a push button and a ratchet mechanism which engages with the upper surface of the container. Depression of the push button urges a push rod to push the container which is adjacent to the inhalation passage of the inhaler, downwards and almost fully out of the sleeve and into the inhalation passage.

A variety of medicaments may be administered by using the inhaler of the invention. Such medicaments are generally antibiotics, bronchodilators or other anti-asthma drugs. Such medicaments include, but are not limited to $ß_2$-agonists, e.g. fenoterol, formoterol, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol and terbutaline; non-selective beta-stimulants such as isoprenaline; xanthine bronchodilators, e.g. theophylline, aminophylline and choline theophyllinate; anticholinergics, e.g. ipratropium bromide; mast cell stabilisers, e.g. sodium cromoglycate and

ketotifen; bronchial anti-inflammatory agents, e.g. nedocromil sodium; and steroids, e.g. beclomethasone dipropionate, fluticasone, budesonide and flunisolide.

Specific combinations of medicaments which may be mentioned include combinations of steroids, such as, beclomethasone dipropionate and formoterol; beclomethasone dipropionate and salmeterol; fluticasone and formoterol; fluticasone and salmeterol; budesonide and formoterol; budesonide and salmeterol; flunisolide and formoterol; and flunisolide and salmeterol. It is also within the scope of this invention to include combinations of one or more of the aforementioned steroids with one or more of the aforementioned $ß_2$-agonists.

Further medicaments which may be mentioned include systemically active materials, such as, proteinaceous compounds and/or macromolecules, for example, hormones and mediators, such as insulin, human growth hormone, leuprolide and alpha interferon; growth factors, anticoagulants, immunomodulators, cytokines and nucleic acids.

The invention will now be described by way of example only and with reference to the accompanying drawings in which,

Figure 1 is a cross section of dosage unit of the invention;

Figure 2 is a perspective view of a dosage unit;

Figure 3 is a perspective view of a dosage unit provided with a single central spacer and a sleeve;

Figure 4 is a perspective view of dosage unit provided with a plurality of spacers and a sleeve and schematically represents the filling, sealing and emptying of the dosage unit;

Figure 5 is a cross-sectional schematic representation of a dosage unit filling process;

Figure 6 is a cross-sectional schematic representation of a cartridge containing dosage units of the invention;

Figure 7 is a cross-sectional schematic representation of a cartridge fitted in an inhaler, e.g. a TECHNOHALER;

Figure 8 is a perspective view of a dosage unit of the invention;

Figure 9 is a perspective cross-sectional view of a dosage unit;

Figure 10 is a perspective view of a sealed dosage unit;

Figure 11 is a perspective view of dosage sealed unit in use;

Figure 12 is a schematic representation of a cartridge comprising dosage units of the invention;

Figure 13 is a schematic representation of a cartridge of the invention illustrating the emptying process.

With reference to figures 1 and 2, a medicament dosage unit (1) comprises a container (2) provided with a closed end (3) and an open end (4). The periphery of the open end (4) is provided with spacers (5). A cap (6) is also shown which comprises a plug with an open end (7) and a closed end (8). In use the closed end (8) of the cap (6) is adjacent to the open end (4) of the container (2). The closed end (8) of the cap (6) is provided with peripheral grooves (9) adapted to engage with the spacers (5), which are provided with a ridge (10) to facilitate engagement.

The container (2) is filled with medicament (11).

Referring to figures 3 and 4, a container (2) slidably engages with a sleeve (12) and is pushed so that only the spacers (5) protrude the end of the sleeve (12). In figure 3 the single, central spacer protrudes from the sleeve, whereas in figure 4, all three spacers protrude from the sleeve. The container (2) may then be filled with medicament (11) and any excess medicament removed, for example, by agitating or shaking the cartridge, the container may then be closed with a cap (6) which is pushed onto the open end (4) of the container (2) such that the container (2) and the cap (6)

slide into the sleeve (12). The closed end (3) of the container (2) protrudes from the sleeve (12) and the sleeve (12) forms a sealing engagement against the joint (13) between the cap (6) and container (2).

In figure 4 the unit may be inverted and a push rod (not shown) urges against the closed end (3) of the container (2) causing it to slide through the sleeve (12) such that the joint (13) protrudes from the sleeve (12) and the cap (6) falls away with the medicament (11) emptying from the container (2).

With reference to figure 5, a cartridge (14) is provided with apertures (15) to receive containers (2). The walls (16) of the apertures (15) form a sleeve (12) around the container (2). The containers (2) are pushed into the sleeves (12) so that the spacers (5) protrude and the open end (4) of the container abuts the periphery (17) of the sleeve (12). Again, medicament (11) may then be poured over the cartridge (14) and any excess medicament removed, for example, by agitating or shaking the cartridge.

With reference to figure 6, the containers (2) are sealed with a cap (6) and the unit is urged into the sleeve (12) so that a seal is formed at the joint (13) between the container (2) and the cap (6).

Referring to figure 7, in use the cartridge (14) is inverted and is placed in a dry powder inhaler (18). The inhaler is provided with a push rod (20) which may be biased with a spring (19).

The push rod (20) pushes against the closed end (3) of the container (2) urging it through the sleeve (12) until the joint (13) protrudes the sleeve (12). The cap (6) falls away and medicament (11) empties into the inhalation passage (21). The cartridge (14) may optionally be rotatably mounted so

that a second container (22) can be brought into contact with the push rod (20).

With reference to figures 8 and 9, a medicament dosage unit (101) comprises a container (102) provided with a closed end (103) and an open end (104). The container (102) is provided with a spacer (105) which protrudes beyond the open end (104). The container (102) is provided with a sleeve (108). The sleeve (108) is also provided with a frangible cover (106) which is adapted to overlie the peripheral edge (107) of the sleeve (108) which is adjacent the open end (104) of the container (102). In use, the container (102) slots into the sleeve (18) and is positioned such that the rim (109) of the container (102) is aligned with the peripheral edge (107) of the sleeve (108).

The container (102) is filled with medicament (111) prior to application of the cover (106). The spacer (105) prevents the medicament (111) from coming into contact with the cover (106) when the cover (106) is applied.

The container (102) is then urged into the sleeve (108) so that the closed end (103) is aligned with the peripheral edge (110) of the sleeve (108). The spacer (105) no longer protrudes from the sleeve (108) and the cover (106) is applied to the sleeve (108), being fixed to the peripheral edge (110).

Referring to figures 10 and 11, the container (102) is slidably mounted within a sleeve (108). The container is inverted so that the closed end (103) of the container (102) is uppermost. When the container (102) is urged towards the frangible cover (106) e.g. by a push rod (not shown) the spacer (105) also acts as a means for breaking the cover (106) allowing the medicament (111) to empty.

Referring to Figures 12a and 12b, a cartridge (112) comprises a plurality of sleeves (108) joined together. In each sleeve (108) is provided a medicament container (102). The cartridge (112) comprises a substantially circular array of sleeves (108) to enable it to be rotatable about a central point, bringing the container (102) in alignment with the inhalation chamber of an inhaler (not shown).

Referring to Figures 13a-d. The containers (102) are aligned in a cartridge (112) so that the rim (1) of the container is aligned with the peripheral edge (107) of the sleeve (108). The cartridge assembly (112) is then filled with medicament (111) so as to fill the containers (102). Any conventionally known filling method may be used, for example, the cartridge may be flooded with medicament and any excess removed or a more focussed filling method may be used. The cartridge may then optionally be placed on a vibrating platform so that any surplus medicament (111) is removed. The containers (102) are then slidably urged through the sleeve (108) so that the spacer (105) no longer protrudes from the open end (104) of the container (102). A foil seal (106) is then fixed to the cartridge over the open ends (104) of the containers (102).

Referring to Figures 14a-c, the cartridge (1112) is filled with medicament (111) and sealed with a foil seal (112). In use, the cartridge is inverted and a push rod (not shown) urges the spacer (105) to break the frangible cover (106) allowing medicament (111) to empty by gravity.

CLAIMS

1. A medicament dosage unit comprising a sleeve and a medicament holding chamber adapted to form a slidable fit within the sleeve, the sleeve and the chamber being dimensioned such that the sleeve extends beyond the length of the chamber, and the unit being provided with an openable closure member.

2. A medicament dosage unit according to Claim 1 characterised in that the dimensions are such that the chamber will be filled to provide a single desired dose.

3. A medicament dosage unit according to Claim 1 characterised in that the chamber is a substantially elongate member with an open end and a closed end.

4. A medicament dosage unit according to Claim 1 characterised in that the chamber is a cylindrical member

5. A medicament dosage unit according to Claim 1 characterised in that the closure member is a removable cap

6. A medicament dosage unit according to Claim 5 characterised in that the cap rests on the sleeve.

7. A medicament dosage unit according to Claim 1 characterised in that the chamber is provided with one or more spacers at its open end.

8. A medicament dosage unit according to Claim 7 characterised in that at least two spacers are present.

9. A medicament dosage unit according to Claim 7 characterised in that the spacers are provided with a ridge upon which the cap may rest.

10. A medicament dosage unit according to Claim 5 characterised in that the cap is substantially the same diameter as the chamber.

11. A medicament dosage unit according to Claim 5 characterised in that the cap comprises a flat disc, a plug or an inverted cup.

12. A medicament dosage unit according to Claim 5 or 7 characterised in that the cap provides a closed face abutting the chamber and/or spacers.

13. A medicament dosage unit according to Claim 5 characterised in that the length of the cap is small relative to the length of the chamber.

14. A medicament dosage unit according to Claim 5 characterised in that the sleeve is adapted to form a snug fit at least around the joint formed between the open end of the chamber and the cap.

15. A medicament dosage unit according to Claim 14 characterised in that the sleeve wraps around the whole of the circumference of the joint so as to form a seal.

16. A medicament dosage unit according to Claim 1 characterised in that the sleeve also acts as a support for the chamber.

17. A medicament dosage unit according to Claim 1 characterised in that the length of the sleeve is substantially the same as the length of the chamber.

18. A medicament dosage unit according to Claim 7 or 17 characterised in that the length of the sleeve is such

that it forms a snug fit with the chamber with only the spacers protruding from the sleeve.

19. A medicament dosage unit according to Claim 1 characterised in that the closure member comprises a cover

20. A medicament dosage unit according to Claim 19 characterised in that the cover is fixed to the sleeve.

21. A medicament dosage unit according to Claim 1 characterised in that the cover is substantially the same diameter as the sleeve.

22. A medicament dosage unit according to Claim 21 characterised in that the cover comprises a frangible material.

23. A medicament dosage unit according to Claim 21 characterised in that the cover comprises a material which is impermeable to moisture and/or is moisture resistant.

24. A medicament dosage cartridge comprising a plurality of dosage units according to Claim 1 connected together.

25. A medicament dosage cartridge according to Claim 24 characterised in that the cartridge comprises a plurality of sleeves arranged around its periphery.

26. A medicament dosage cartridge according to Claim 25 characterised in that the sleeves are connected together.

27. A medicament dosage cartridge according to Claim 26 characterised in that the units are permanently attached to one another.

28. A medicament delivery device comprising medicament a dosage unit according to claim 1

29. A medicament delivery device according to Claim 28 characterised in that the delivery device is an inhaler.

30. A medicament delivery device according to Claim 29 characterised in that the inhaler is a dry powder inhaler.

31. A medicament delivery device according to Claim 30 characterised in that the inhaler is provided with a plurality of medicament dosage units in the form of a cartridge.

32. A medicament delivery device according to Claim 31 characterised in that the device is provided with suitable indexing means.

33. A method of delivering a medicament which comprises using a delivery device according to Claim 1.

34. A method of administering a dry powder medicament using a delivery device according to Claim 28.

35. A method according to claim 34 characterised in that the devise is an inhaler.

36. A method of treatment of a patient with a disorder comprising the administration of a therapeutically effective amount of a medicament using an inhaler according to claim 29.

37. A method according to claim 36 characterised in that the disorder is a respiratory disorder.

38. A medicament dosage unit or a delivery device substantially as described with reference to the accompanying drawings.

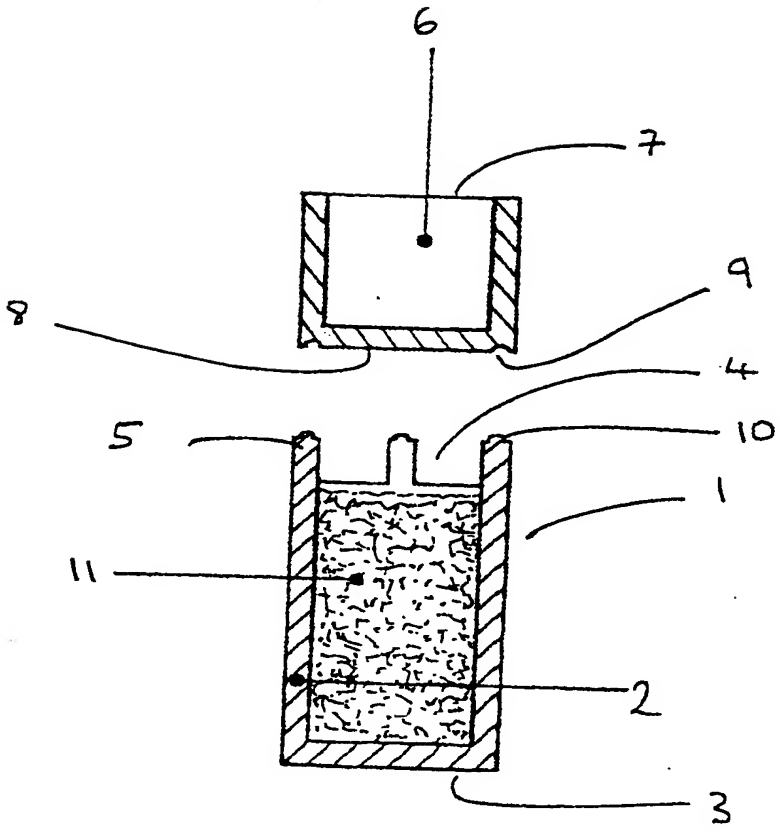


Fig. 1

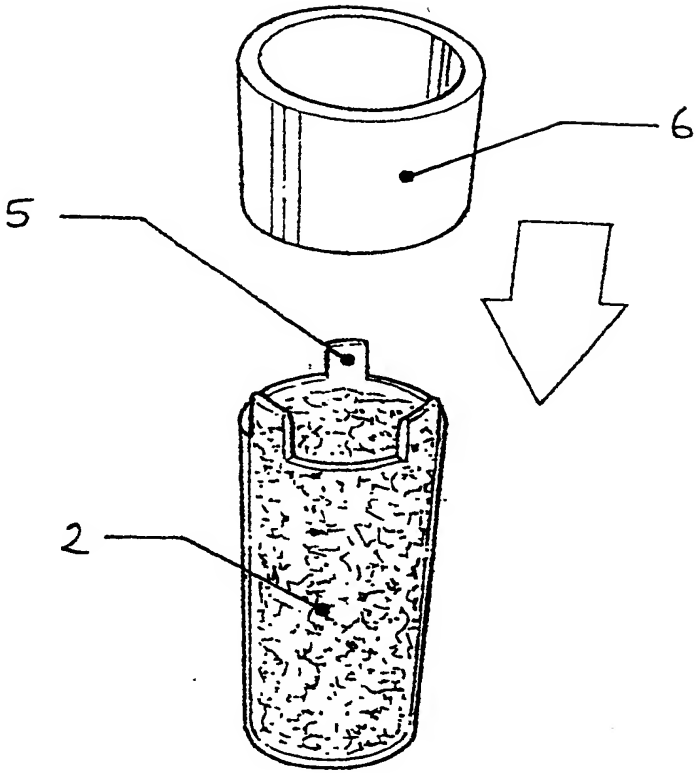


Fig. 2

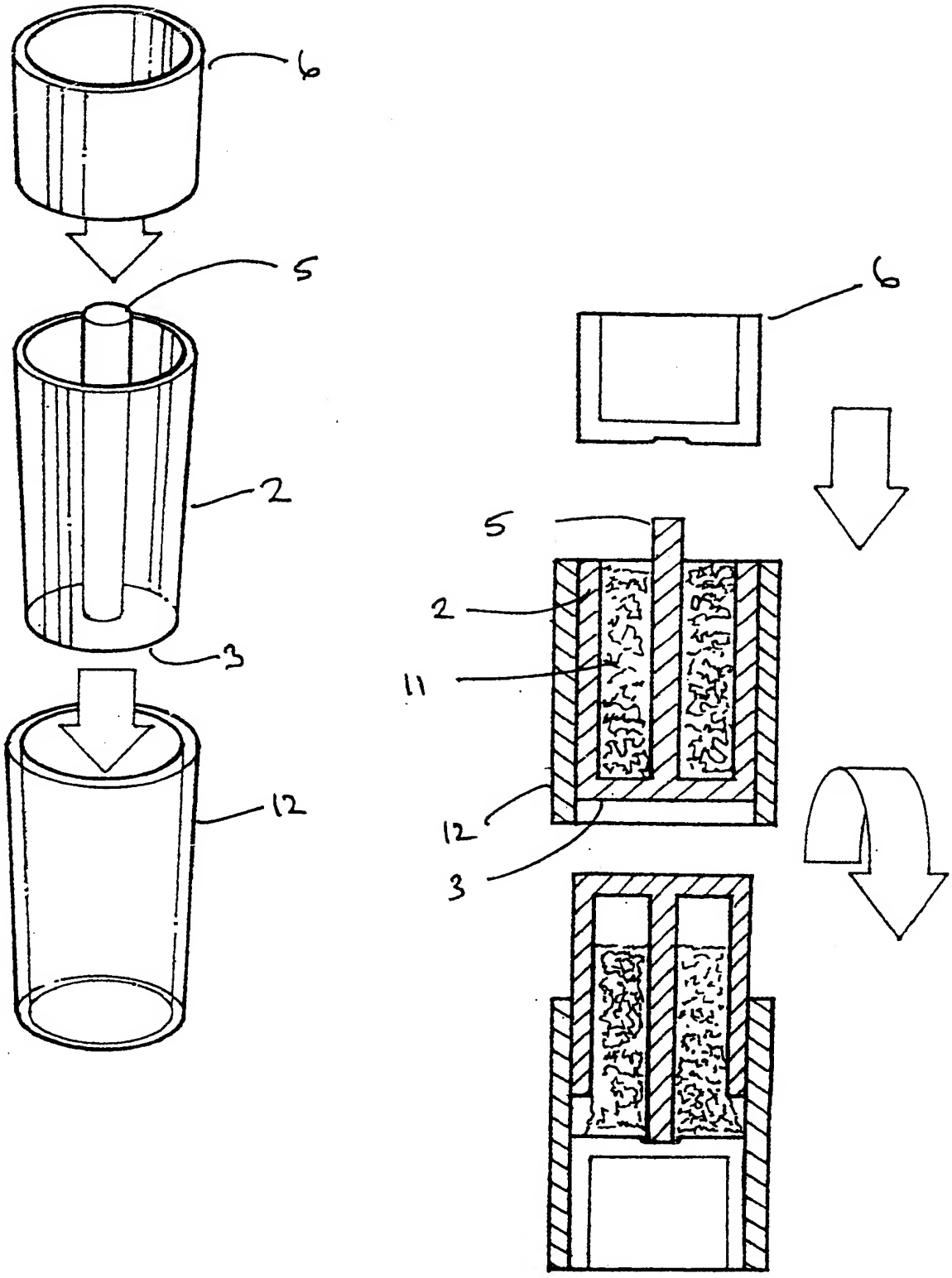


Fig. 3

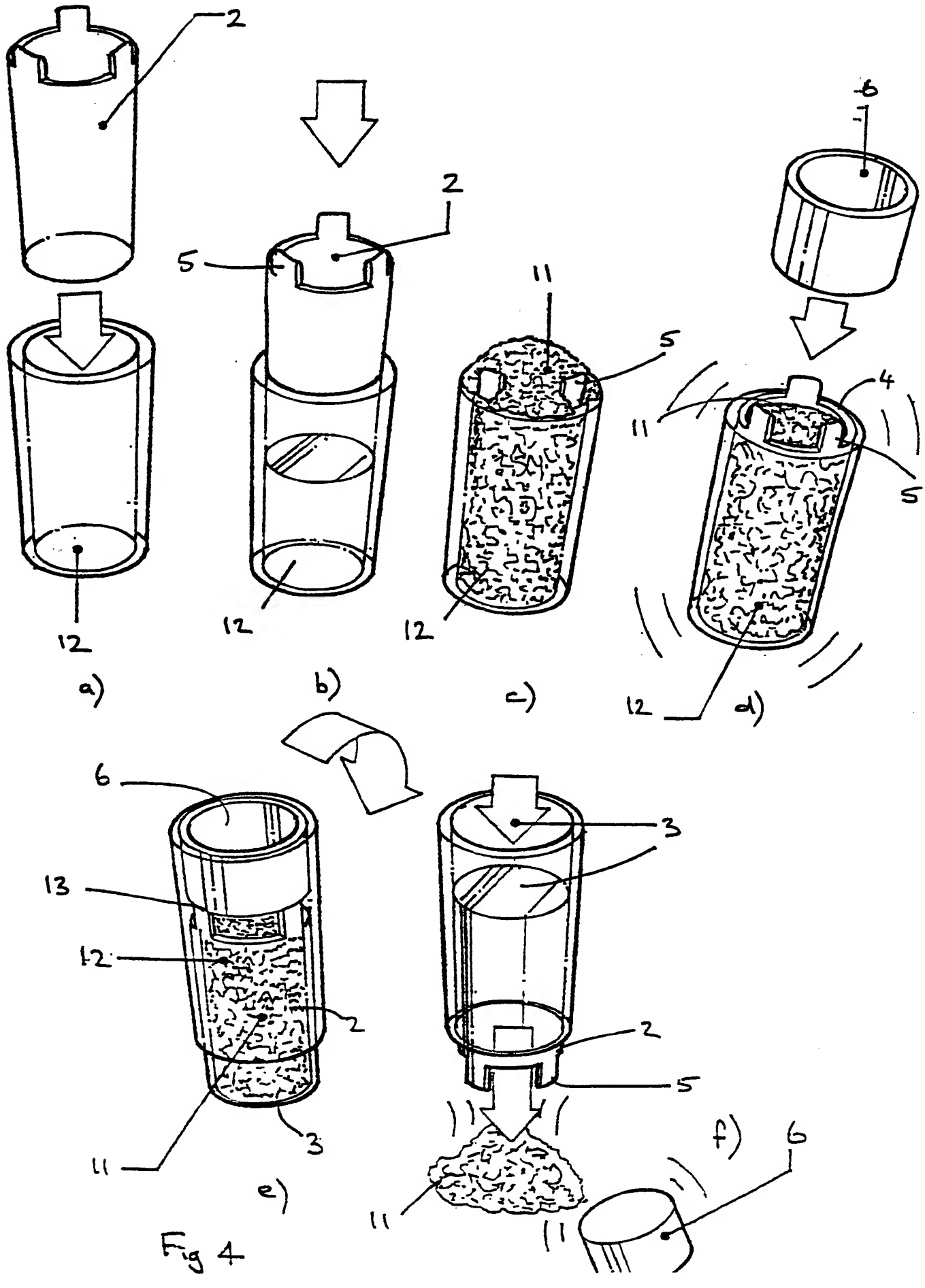
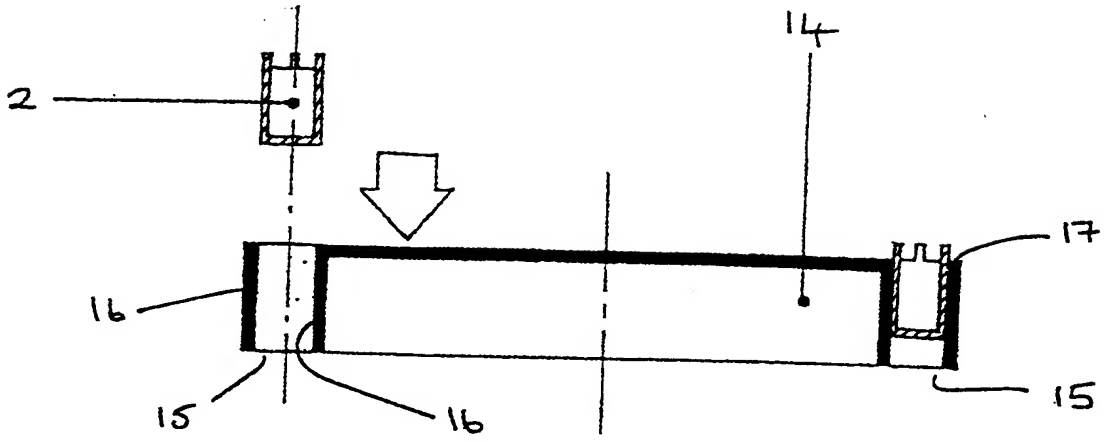


Fig 4



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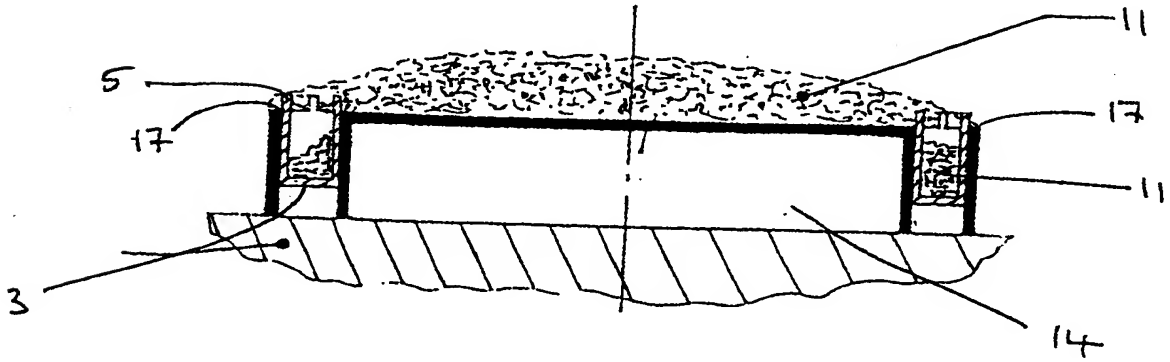

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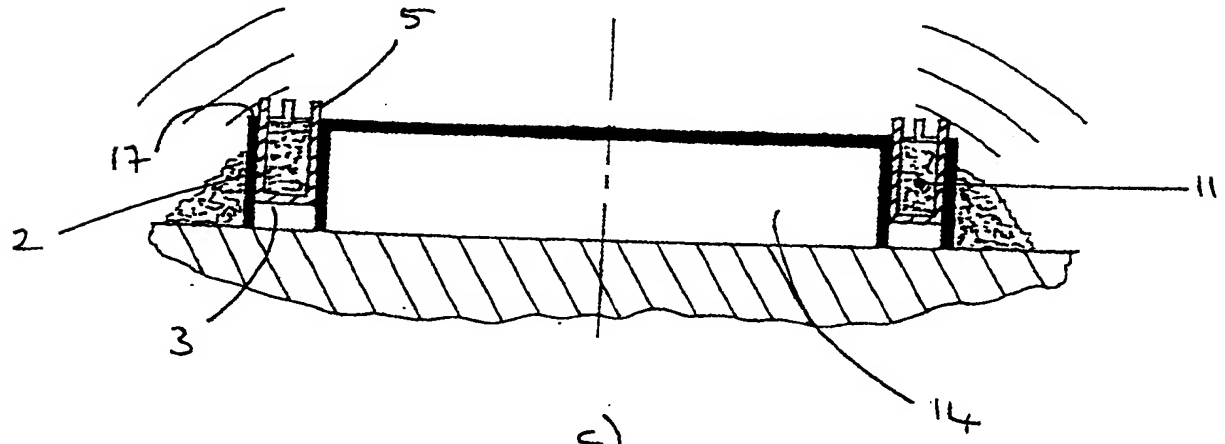

c)

Fig. 5

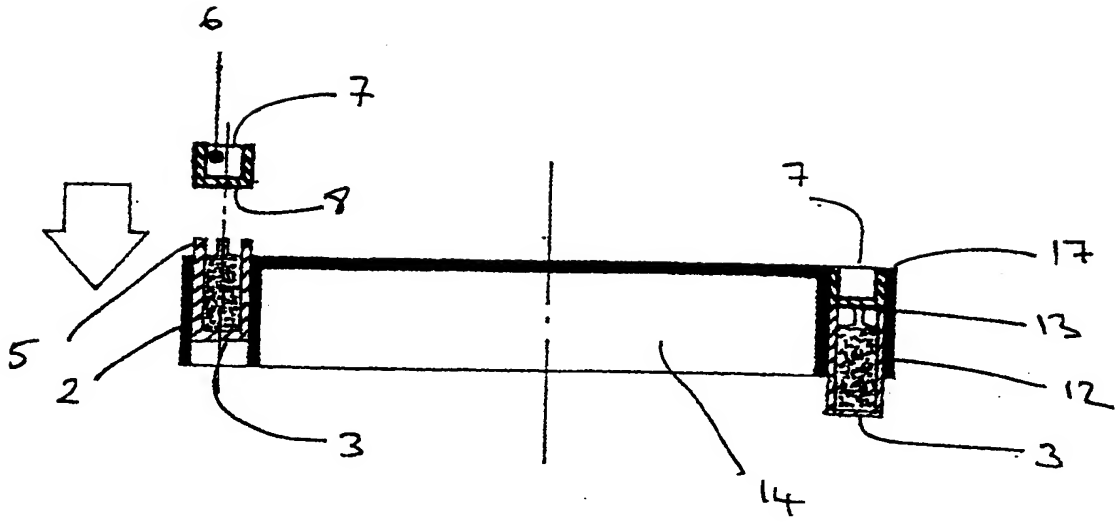
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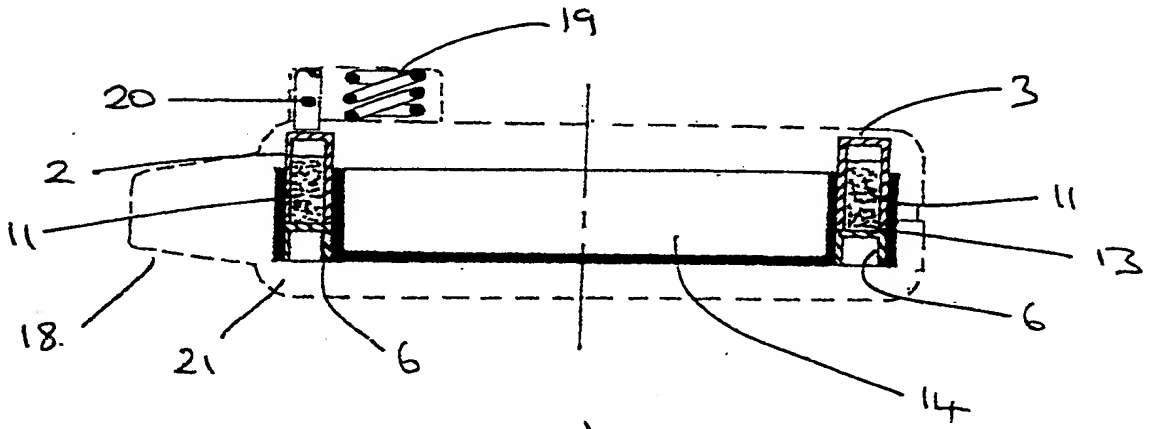
Fig 6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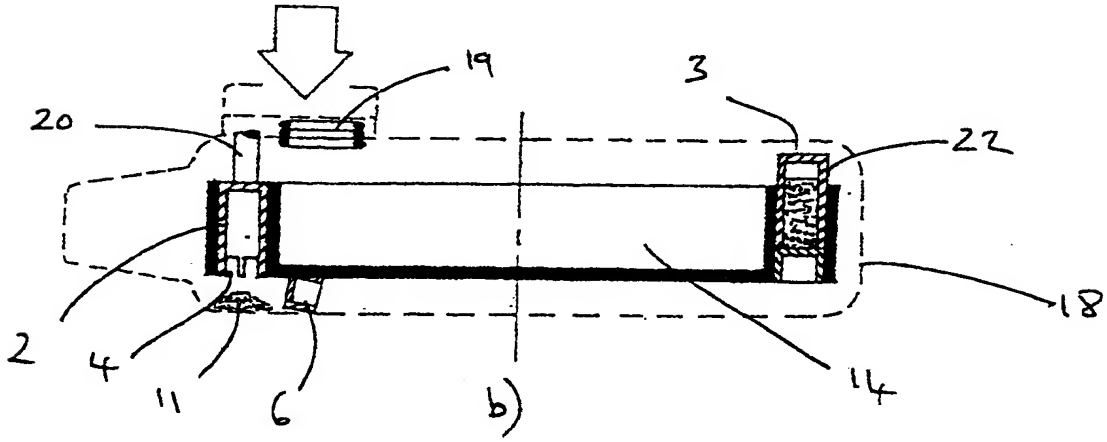
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b)

Fig 7

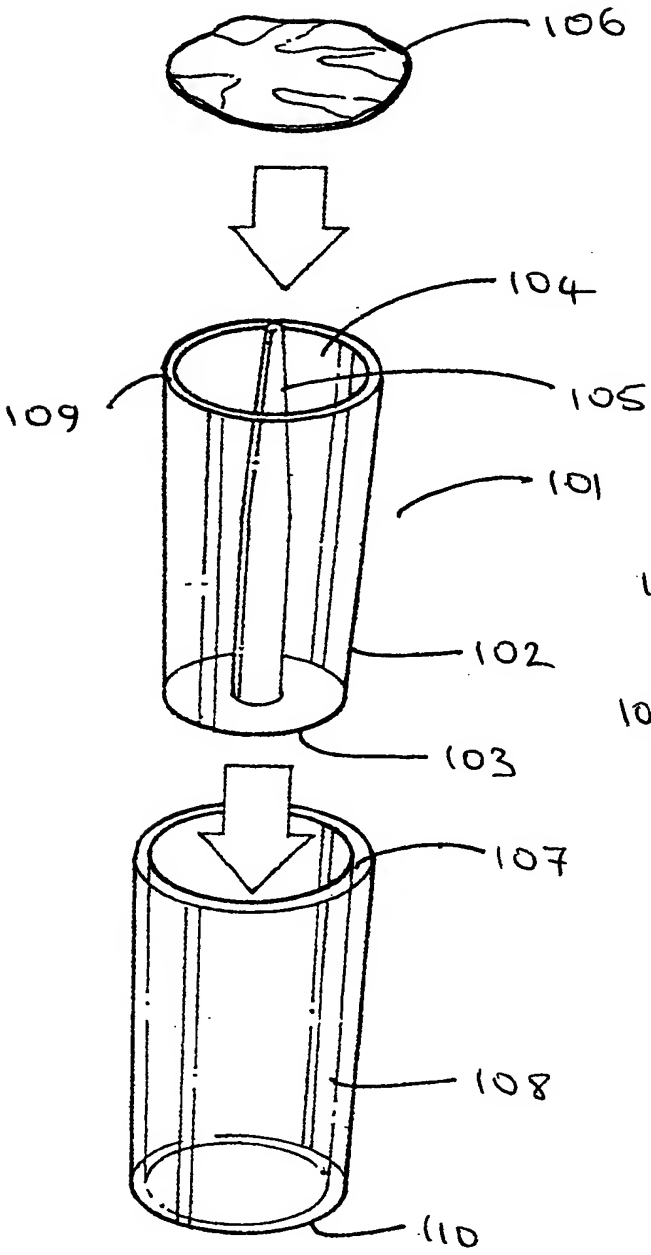
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Fig. 8

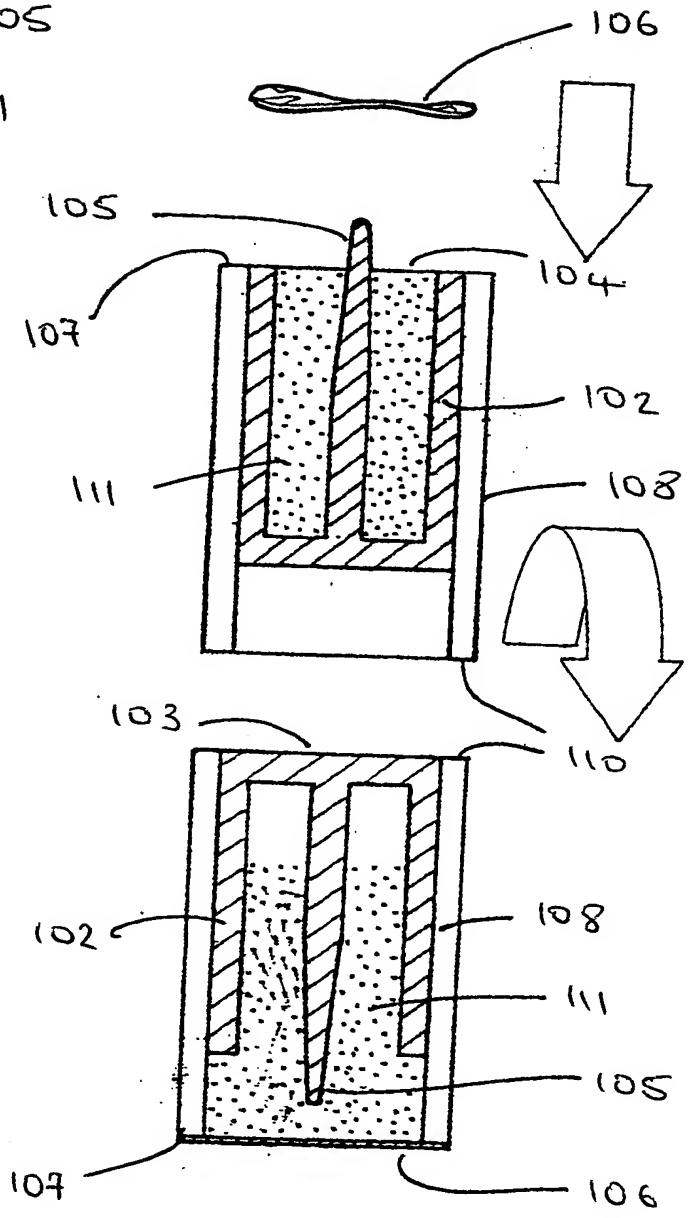
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Fig. 9

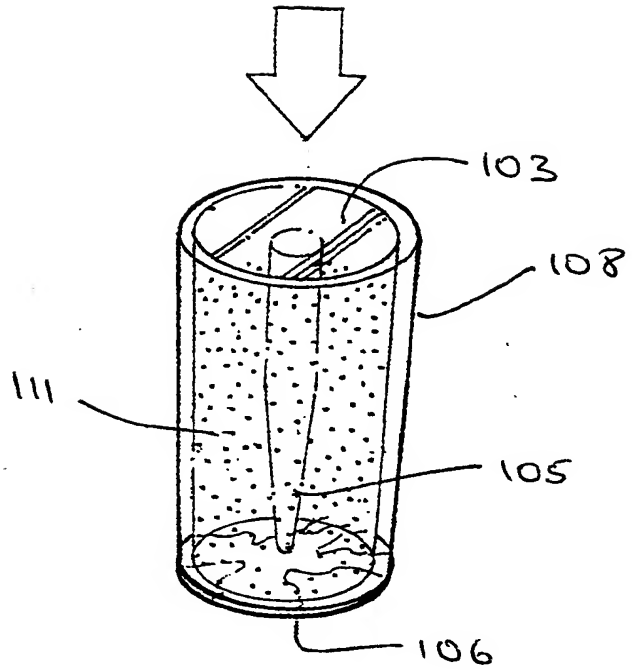

Fig. 10

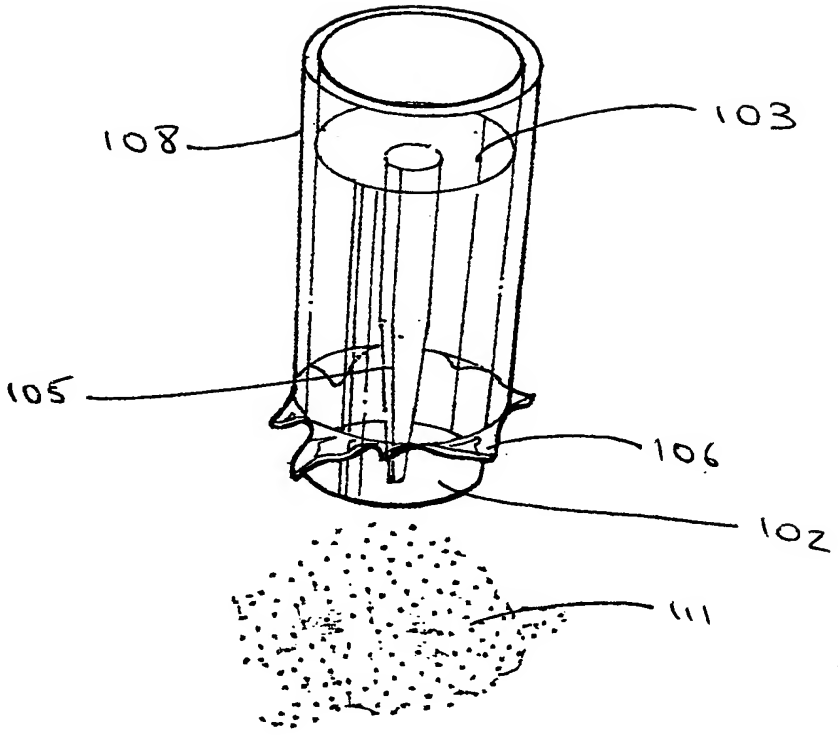

Fig. 11

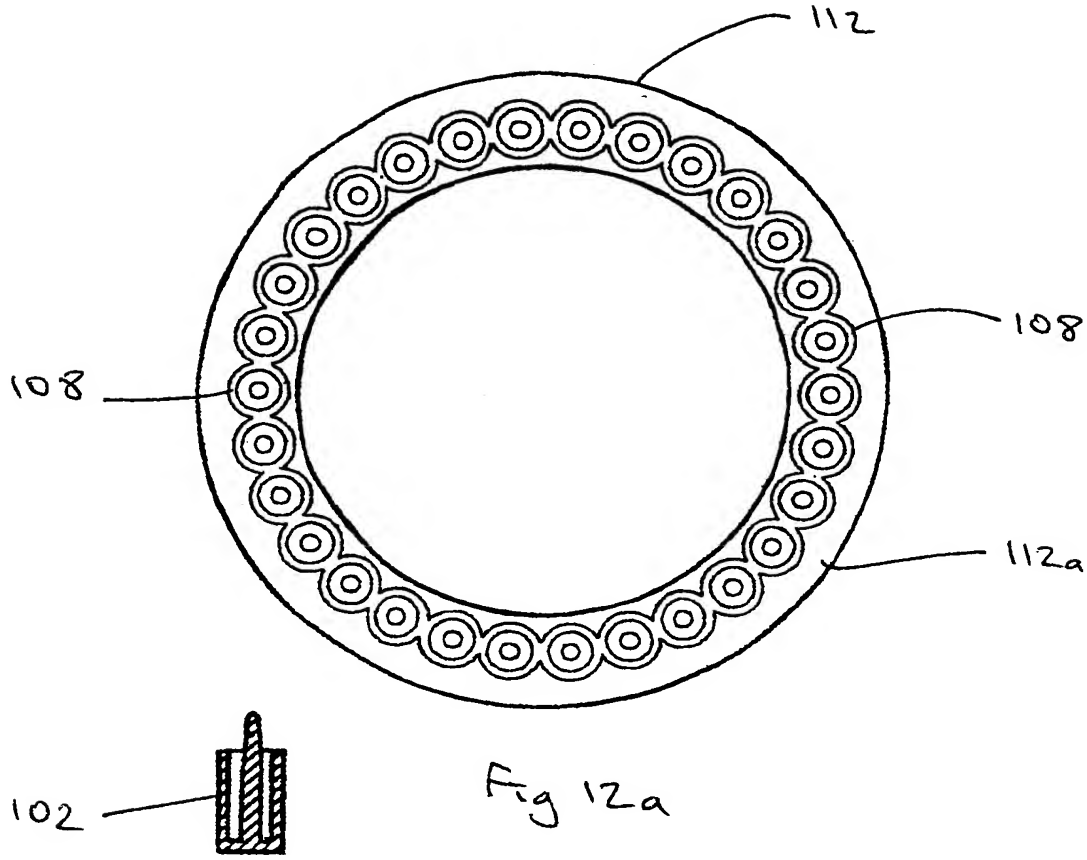

Fig 12a

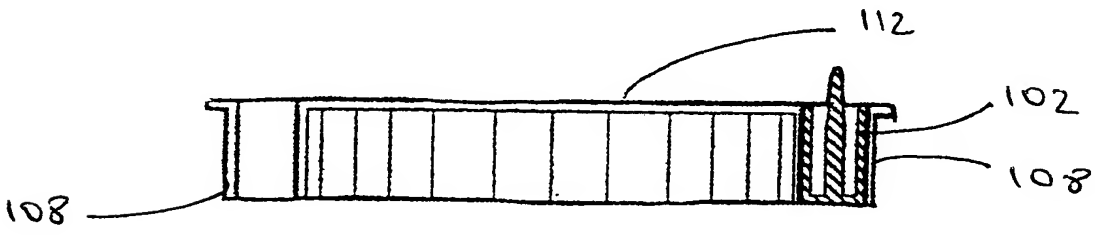

Fig 12b

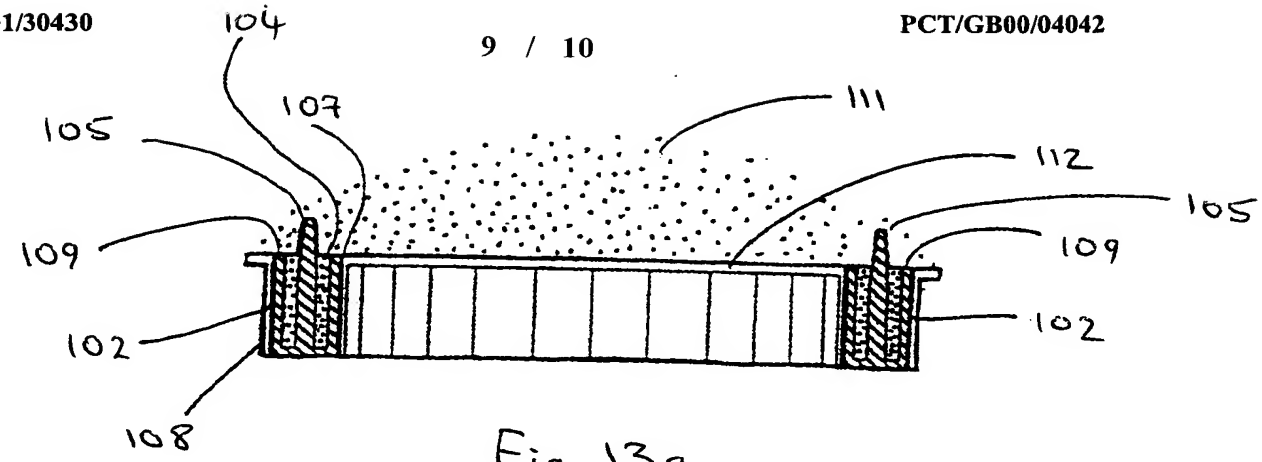

Fig 13a

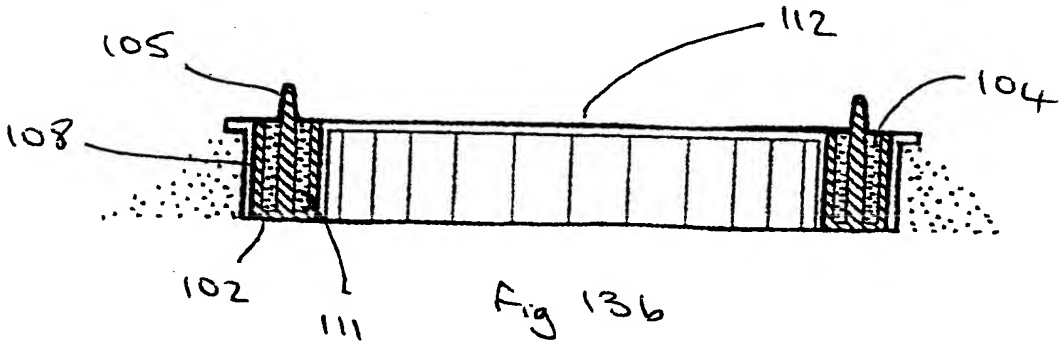

Fig 13b

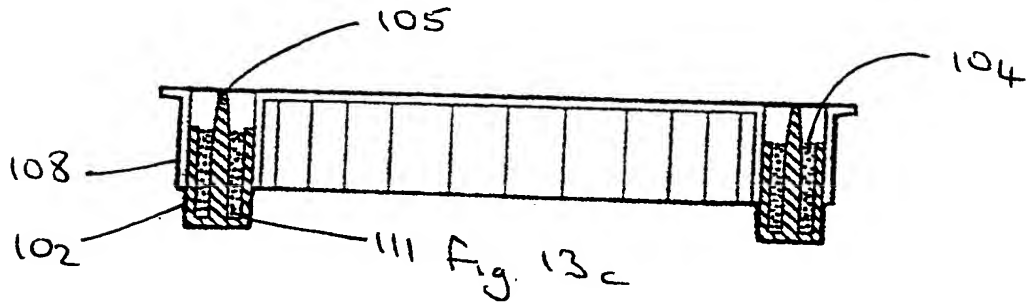

Fig 13c

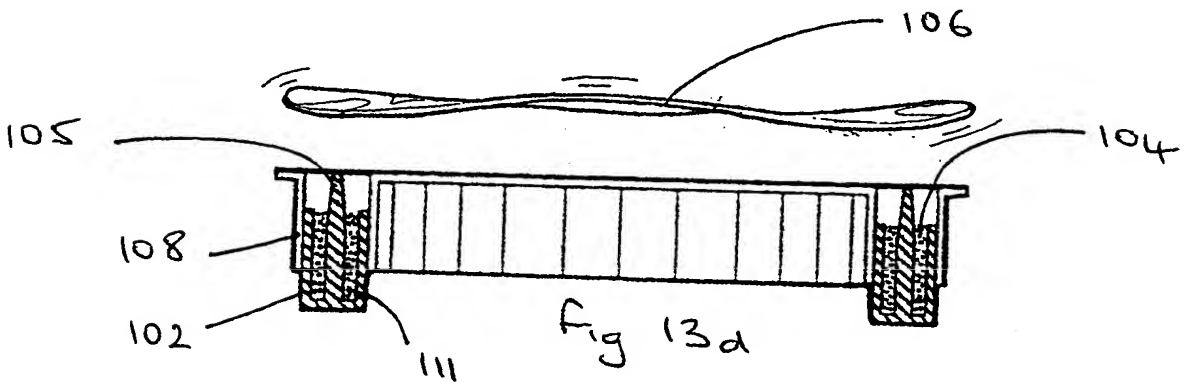

Fig 13d

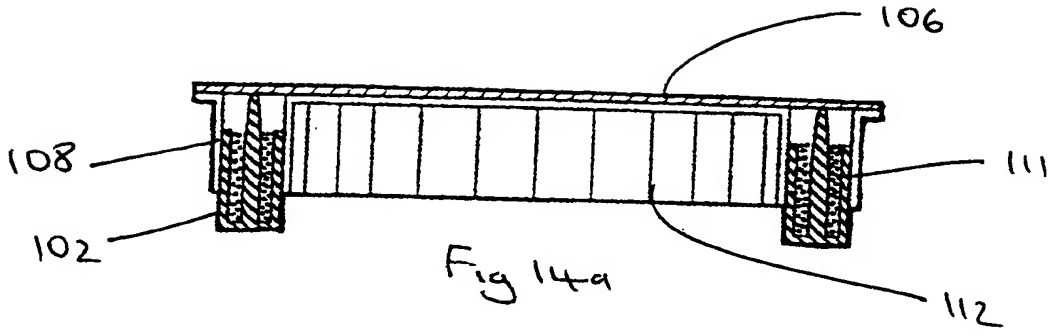

Fig 14a

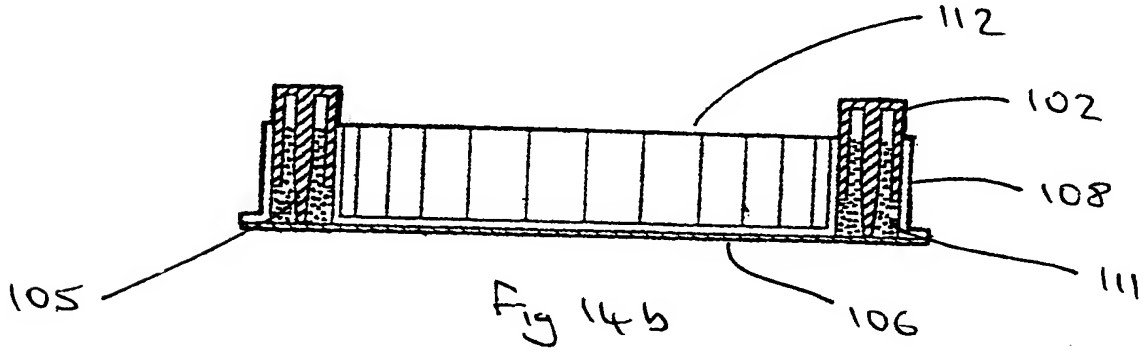

Fig 14b

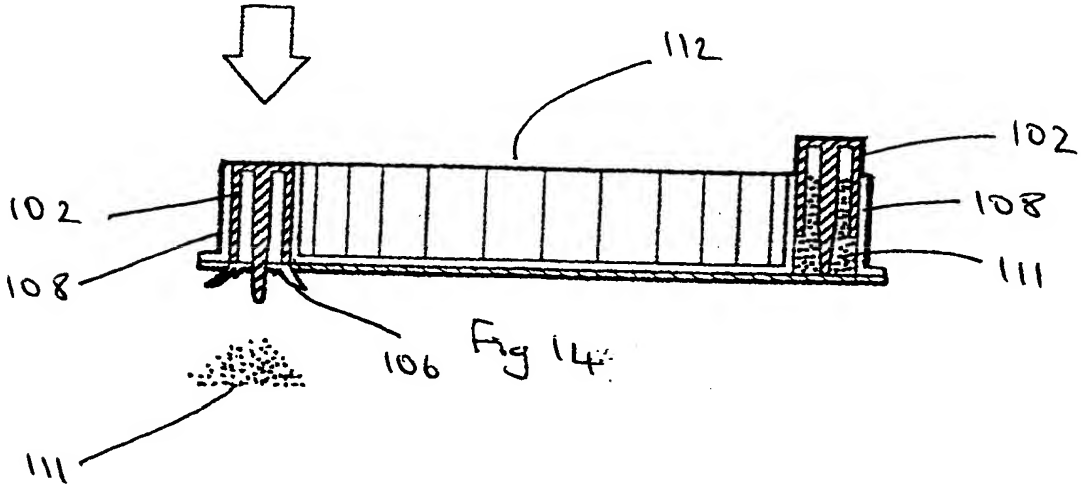

Fig 14c

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/GB 00/04042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00 A61J1/03 A61J3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 411 175 A (VENUS JR FRANK ET AL) 2 May 1995 (1995-05-02)	1-4,16, 17, 19-24, 28,33,38
Y	column 5, line 38-49	25-27, 29-32, 34-37
A	column 5, line 63 -column 6, line 2 column 7, line 11-21 column 9, line 3-5; figures 6-11,20	10-12
Y	WO 93 16748 A (INNOVATA BIOMED LTD) 2 September 1993 (1993-09-02)	25-27, 29-32, 34-37
A	page 33, line 7 -page 34, line 17 page 35, line 29 -page 37, line 16; figures 16,17,19,20	28,33

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2001	30/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Balz, O

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/GB 00/04042

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 5 562 918 A (STIMPSON PHILIP G) 8 October 1996 (1996-10-08) column 12, line 1 -column 13, line 66; figures 18-27	1-6,10, 13-17, 19-38
A	US 3 439 823 A (MORANE BRUNO) 22 April 1969 (1969-04-22) the whole document	1-6, 10-16

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Information on patent family members

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